Hormone Therapy and Age-Related Macular Degeneration

The Women’s Health Initiative Sight Exam Study

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Objective: To determine the effectiveness of treatment with conjugated equine estrogens (CEE) or with CEE combined with progestin (CEE + P) on age-related macular degeneration (AMD).

Methods: In an ancillary study to the Women’s Health Initiative clinical trial of hormone therapy, 4262 women 65 years and older underwent fundus photography for the determination of AMD. Participants were recruited from April 2000 to June 2002 at 21 clinical sites an average of 5 years after randomization. Participants were randomized to treatment with CEE, CEE + P, or placebo. Participants had been treated for an average of 5 years at the ophthalmic evaluation for AMD.

Results: The overall prevalence of any AMD was 21.0%. No association was found between CEE + P (odds ratio [OR], 0.91; 95% confidence interval [CI], 0.75-1.11) or CEE alone (OR, 0.98; 95% CI, 0.78-1.25) and early-stage AMD. The CEE + P was associated with a reduced risk of soft drusen (OR, 0.83; 95% CI, 0.68-1.00) after adjustment for covariates and with a reduced risk of neovascular AMD (OR, 0.29; 95% CI, 0.09-0.92).

Conclusions: Treatment with CEE alone or CEE + P does not affect early- or late-stage AMD. Treatment with CEE + P may reduce the risk of soft drusen or neovascular AMD.

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The women in this study were recruited between April 2000 and June 2002 from those 65 years or older who were enrolled in 1 of 21 clinical sites in the WHI CT of HT. To be eligible for the WHISE Study, a woman had to be 65 years or older at her eye examination and have at least 1 eye that could be photographed using standard methods. Participants who did not have a hysterectomy before enrollment into the WHI HT CT were randomly assigned to either conjugated equine estrogens with progestin (CEE + P) (0.625 mg/d of CEE and 2.5 mg/d of progestin) or a placebo. Those without a uterus were randomly assigned to either CEE (0.625 mg/d) or a placebo. Participants in the WHISE Study were recruited an average of 5.1 (median, 5.0; range, 1-10) years after randomization into the WHI HT CT. Participants included 4688 women who consented to participate in the WHISE Study; 4349 completed enrollment with photographs of at least 1 eye, 96.6% of the enrollment goal of 4500 participants. The study was originally designed to conduct a second eye examination to capture incidence. However, the sponsor canceled the study in the wake of the WHI HT CT main study results and the second examination could not be done.

MEASUREMENTS

Eye Assessment

At the WHI clinic, participants completed a questionnaire that collected ocular and medical history on conditions such as cataracts, glaucoma, diabetes mellitus, early and late AMD, retinal detachment, trauma, and previous treatment or ocular surgery.
Fundus Photographs

After pupillary dilation to at least 6 mm, the photographer took 30° or 35° stereoscopic fundus photographs. Fundus photographs were taken following a specified protocol that was adapted for this study by photography consultants at the University of Wisconsin.2 Participants without diabetes mellitus were photographed using a modified 3–standard field protocol; 2 stereoscopic fundus photographs of the modified optic disc field (Early Treatment Diabetic Retinopathy Study field 1M), 2 of the modified macula field (Early Treatment Diabetic Retinopathy Study field 2M), and an additional nonstereoscopic photograph temporal to the macula (Early Treatment Diabetic Retinopathy Study field 3M) were taken. Participants with diabetes mellitus had photographs taken of the 7 standard fields, consisting of 2 stereoscopic photographs of each of the following fields: optic disc, macula, temporal to macula, superior temporal, inferior temporal, superior nasal, and inferior nasal. If the participant had evidence of new vessels or a preretinal or vitreous hemorrhage, an additional photograph was taken to document the lesion. All participants had 2 fundus (red reflex) photographs taken to allow the Reading Center’s graders to take opacities of the media into consideration when reviewing photographic quality.

Fundus Photography Grading

Grading of the fundus photographs was performed using a modification of the Wisconsin Age-Related Maculopathy Grading System.21 The grading system involved a preliminary grading and then detailed grading of each set of photographs followed by an editing/adjudication procedure if conflicting results were obtained. Graders were masked to visual acuity and eye examination results. During preliminary grading, overall photograph quality was graded and drusen, pigment abnormality, and late AMD measurements were recorded. The presence of a retinal condition, such as dystrophy, vessel occlusion, trauma, or non-AMD retinal detachment, or an inflammatory condition affecting the ability to grade the macula for AMD excluded a set of photographs from grading for early or late AMD. The grading protocol entails evaluation of the presence, size, and type of drusen and retinal pigment epithelial abnormalities. Drusen were classified in order of severity as follows: hard indistinct, hard distinct, soft indistinct, and soft indistinct or reticular. Drusen size was classified in order of increasing maximum size (0, <63, ≤125, <230, and ≥230 µm). Drusen area was measured as total combined area for all drusen types present in the grid. Retinal pigment epithelial depigmentation and increased retinal pigment component lesions of pigmentary abnormalities, were measured as present or absent. Characteristic lesions of advanced AMD, such as geographic atrophy, neovascular AMD, increased retinal pigment, pigment epithelial detachment/detachment of sensory retina, subretinal hemorrhage, subretinal fibrous or glial scarring, and evidence of local ablative photocoagulation treatment, were also identified and reported.

STUDY OUTCOMES: EARLY AND LATE AMD

The primary study outcome was any AMD. Each eye was classified for severity of AMD based on a 6-level scale21 (Table 1). The categories were as follows: no AMD, minimal early AMD, moderate early AMD, severe early AMD, and 2 stages of late AMD (geographic atrophy and neovascular AMD). If a participant had AMD in both eyes, the eye with the most advanced AMD was used for the analysis. Of 8694 eyes photographed, 94.5% had a left and a right eye photograph; 6 left and 6 right eyes had no photograph, and 139 left eyes and 145 right eyes were notgradable. Participants with an ungradable photograph were excluded from the analysis. Those with only 1 eye were included if the existing eye had a gradable photograph. “Any AMD” coding included any stage of AMD. Any “early AMD” included minimal, moderate, and severe early AMD. When analyses involved early AMD, those with late AMD were excluded and vice versa.

We also examined late AMD and several intermediate outcomes. Late AMD was defined as pure geographic atrophy and/or neovascular AMD. Neovascular AMD was defined as exudative macular degeneration with or without geographic atrophy present vs no AMD. Any soft drusen was defined as soft distinct drusen, soft indistinct drusen and reticular drusen, or hard distinct and hard indistinct drusen vs no drusen. The no drusen category included only those with no drusen, questionable drusen, and drusen smaller than 63 µm. Increased pigmentation was defined as the presence of increased pigmentation, and retinal pigment epithelial depigmentation was defined as the presence of retinal pigment epithelial vs no pigmentary changes.

STATISTICAL ANALYSIS

The trial design for the parent study has been published elsewhere.27 The WHISE Study design involved assessment of participants for early or late AMD an average of 5 years after randomization in the main trial. There was no prerandomization assessment for AMD. The WHISE Study participants were asked whether and when they were diagnosed as having AMD. This information was used to exclude participants who reported an AMD diagnosis before randomization from analyses. An analysis combining the 2 trials was attempted, and there was no change in the association between treatment and any AMD outcome. Therefore, we retained an analysis by trial because it was more consistent with the design of the parent study.

For each trial, the intention-to-treat analysis compared the unaadjusted risk of AMD outcomes in the active treatment groups with that in the placebo group. Post hoc multivariate analysis

| Table 1. The AMD Grading System Used at the WHISE Study Baseline Examination |
|-----------------------------|-----------------------------|-----------------------------|
| AMD Level | Classification | Description |
| 1 | No AMD | No signs of any AMD lesions or hard or soft drusen smaller than 63 µm, without pigmentary abnormalities |
| 2 | Minimal early AMD | Soft drusen 63 µm in diameter or greater, with an area of drusen smaller than 196 350 µm² and no pigmentary abnormalities or soft drusen smaller than 63 µm, without pigmentary abnormalities; no signs of late AMD |
| 3 | Moderate early AMD | Soft drusen that are 125 µm in diameter or greater, with an area of drusen that is 196 350 µm² or greater, and no pigmentary abnormalities or soft drusen that are 125 µm in diameter or greater, with an area of drusen that is smaller than 196 350 µm², with pigmentary abnormalities; no signs of late AMD |
| 4 | Severe early AMD | Soft drusen that are 125 µm in diameter or greater, with an area of drusen that is 196 350 µm² or greater, with pigmentary abnormalities present; no signs of late AMD |
| 5 | Dry late AMD | Signs of geographic atrophy |
| 6 | Wet late AMD | Signs of exudative macular degeneration |

Abbreviations: AMD, age-related macular degeneration; WHISE, Women’s Health Initiative Sight Exam.
was then used to assess for confounding. A series of logistic regression models was used to test the associations between randomization assignment and the outcomes.

The primary planned outcome in this study was any AMD. The original design called for a combined analysis of CEE with CEE + P trial. A 3% expected prevalence of AMD and an annual incidence of 3% to 4% was assumed. At protocol development, only 2 adequately designed observational studies had been published examining the effects of hormone therapy on AMD. One of these studies reported a similar reduction in women 65 years and older because the expected prevalence and annual incidence of AMD in younger women would be low, resulting in lower power. Because of study discontinuation, we were unable to obtain incidence information. We reached 96.6% of our intended goal of 4500 eligible and consenting participants.

Analyses of adherence defined nonadherence as any of the following: discontinued study medications, crossed to the placebo group or another hormone, or decreased below the 80% compliance based on pill counts at any time during follow-up. Analyses for the 2 WHI HT trials (CEE vs placebo and CEE + P vs placebo) were done separately. SAS statistical software, version 9.0 (SAS Institute Inc, Cary, NC), was used for analyzing the data. Subjects with a self-reported physician diagnosis of any AMD at baseline and those with ungradable fundus photography for both eyes were excluded from this analysis.

WHISE STUDY SAMPLE CHARACTERISTICS

Of 4688 consenting subjects, 426 were excluded from the study analyses; of these subjects, 310 withdrew from the study before study enrollment, 26 were ineligible, 59 had ungradable photographs, 5 died before they could complete enrollment in the study, and 26 were excluded from analyses because they reported having an AMD diagnosis before randomization. The final analysis included 4262 participants. There were 2635 participants in the CEE + P trial and 1627 in the CEE trial. In the CEE + P trial, 52.3% were receiving active treatment and 47.7% were receiving placebo. In the CEE trial, 48.1% were receiving active treatment and 51.9% were receiving placebo. Adherence was significantly lower in the active treatment arm in both trials, although there was less difference in the CEE trial (46.2% in the active arm vs 57.5% in the placebo arm) than in the CEE + P trial (36.2% in the active arm vs 41.1% in the placebo arm). Adherence in the WHISE Study is a reflection of adherence in the parent study.

As reported elsewhere, there were no differences within each trial by randomization assignment for age, age at menarche or menopause, education, race, annual income, smoking, alcohol consumption, diabetes mellitus, stroke, myocardial infarction, peripheral artery disease, glaucoma, cataract, or history of hormone use. The WHISE Study subsample did not differ from the parent study sample in this regard.

The overall prevalence of any AMD was 21.0% (893/4262). The prevalence of any AMD was higher at older ages: 14.7% among those aged 65 to 69 years, 20.1% in those aged 70 to 74 years, and 29.8% in those aged 75 years or older. There were 366 women with any AMD in the CEE trial and 527 in the CEE + P trial. The number of late (neovascular or geographic) AMD cases was small (18 in the CEE trial and 28 in the CEE + P trial). There were 261 cases in which women had any AMD in the right eye alone, 300 cases of any AMD in the left eye alone, and 332 cases of any AMD in both eyes. The number of cases of late AMD was too small to permit reliable and stable estimates, so no odds ratios are shown.

Table 2 shows the results of an intention-to-treat analysis with a series of logistic regression models testing the association between treatment assignment and AMD outcomes within each trial. The table displays 2 models, 1 with only randomization assignment and 1 that is fully adjusted, including randomization, age at randomization, adherence, and age at menopause.

Within the CEE trial, there were no statistically significant associations for the association between treatment and early AMD in the unadjusted model. Adjustment for age, adherence, and age at menopause did not affect the associations between treatment and any of the outcomes.

Within the CEE + P trial analysis, there were no significant differences in the risk of any of the outcomes in the unadjusted models. After adjustment for age at randomization, adherence, and age at menopause, treatment was marginally associated with a small reduction

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**Table 2. The Effect of Hormone Therapy on Different Stages of AMD**

<table>
<thead>
<tr>
<th>Model</th>
<th>Treated/Placebo Group (n = 782/845)</th>
<th>OR (95% CI)</th>
<th>Treated/Placebo Group (n = 1379/1256)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any early AMD</td>
<td>166/182</td>
<td>0.98 (0.78-1.25)</td>
<td>0.99 (0.78-1.26)</td>
<td>252/247</td>
</tr>
<tr>
<td>Any soft drusen</td>
<td>243/257</td>
<td>1.03 (0.83-1.27)</td>
<td>1.05 (0.84-1.30)</td>
<td>387/380</td>
</tr>
<tr>
<td>Increased pigmentation</td>
<td>59/69</td>
<td>0.92 (0.64-1.32)</td>
<td>0.92 (0.63-1.32)</td>
<td>92/80</td>
</tr>
<tr>
<td>RPE depigmentation</td>
<td>29/29</td>
<td>1.08 (0.64-1.83)</td>
<td>1.14 (0.67-1.94)</td>
<td>47/40</td>
</tr>
<tr>
<td>Late AMD</td>
<td>9/9</td>
<td>1.08 (0.43-2.73)</td>
<td>1.15 (0.45-2.98)</td>
<td>13/15</td>
</tr>
<tr>
<td>Geographic atrophy</td>
<td>3/2</td>
<td>1.62 (0.27-9.71)</td>
<td>NA†</td>
<td>6/2</td>
</tr>
<tr>
<td>Neovascular late AMD</td>
<td>6/7</td>
<td>0.92 (0.31-2.76)</td>
<td>1.02 (0.34-3.12)</td>
<td>7/113</td>
</tr>
</tbody>
</table>

Abbreviations: AMD, age-related macular degeneration; CEE, conjugated equine estrogen; CEE + P, CEE plus progestin; CI, confidence interval; NA, data not applicable (no cases); OR, odds ratio; RPE, retinal pigment epithelial.

†No cases.
in the risk of any soft drusen. Compared with women receiving placebo, women receiving active treatment had an almost 20% lower risk of any soft drusen. The confidence limits for both of these comparisons were wide and barely included 1.0. Treatment with CEE + P was associated with a lower occurrence of neovascular AMD.

**COMMENT**

We conclude that treatment with hormones does not influence the occurrence of early AMD. As an exception, a possible protective effect was found for soft drusen or neovascular AMD in relation to CEE + P. We also found that CEE + P may offer a protective effect for neovascular AMD. Our finding of a protective effect for neovascular AMD is consistent with a case-control study\(^6\) that found a protective effect for CEE use but did not evaluate unopposed vs combination therapy. Cumming and Mitchell\(^2\) reported a lower risk of AMD in women using hormone therapy. A recent article by Freeman et al\(^7\) found a reduced risk of large drusen but not AMD associated with HT use.

We measured AMD in the WHISE trial an average of 5 years after randomization into the WHI HT CT. Because of early discontinuation of both trials by the National Institutes of Health because of safety concerns or lack of efficacy and cancellation of the WHISE Study by the sponsor, we were not able to follow up for incidence or progression of AMD in the women in the trial. We did not have photographs taken before randomization, and we cannot be completely certain which women had disease at WHI randomization and which developed disease after randomization. However, we excluded women from the analysis who reported that they had an AMD diagnosis by a physician at dates preceding WHI randomization. These were probably more advanced cases that had been detected. There were no AMD cases from fundus photography in women whose time from randomization to enrollment in the WHISE Study was less than 2 years. Of the early to moderate AMD cases, 64% were found in the fifth year or later from WHI randomization. Work on progression of AMD suggests that a greater than 5-year time frame is sufficient for development of incident disease.\(^28\)-\(^30\)

There were no differences at WHI baseline in cardiovascular conditions by treatment arm within either trial among the WHISE Study participants, so these factors did not confound the association with treatment and neovascular AMD. Although women in the main trial who were receiving CEE + P active treatment tended to drop out of treatment during the study, the WHISE Study did not exclude them and the adherence data for the WHISE Study did not differ from those of WHI HT CT. Compliance in the overall trial could have reduced the effect of treatment on our outcome.

Extensive evidence\(^28\)-\(^32\) has strongly supported the notion that early AMD and soft drusen are associated with increased risk of late-stage AMD, visual impairment, and progression to larger drusen. In this study, we have some modest evidence linking exposure to CEE + P with a reduced risk of soft drusen. If this treatment does reduce the development of soft drusen, it could be beneficial for prevention of late-stage disease. While the benefits of treatment for neovascular disease seem to be strong, the number of neovascular cases in this study is quite small and the estimate is unstable. Treatment with CEE does not seem to provide any benefit or harm for early-stage AMD.

The prevalence of AMD in our study was 21.0%, somewhat higher than reported in one study of AMD among older women (15% prevalence of any AMD in white women \(\geq 70\) years) and lower than the 27% found among white women aged 65 to 86 years in the Beaver Dam Eye Study. \(^33\),\(^34\) Women enrolled in the WHI HT CT may have volunteered for the WHISE Study because of a previous diagnosis, a family history of AMD, or concerns with visual functioning. Conversely, if women had significant visual limitations, they may have been less likely to participate in the main WHI HT CT or might have been screened out because of the extensive reading and writing required for completing baseline survey forms. The induction time required for treatment with HT to influence AMD is not known; it is possible that exposure for longer than 5 years is required to demonstrate benefits or harm from treatment. The ability of treatment to influence AMD may be greater at ages younger than 65 years.

A few other studies have suggested that postmenopausal hormone treatment reduces the risk of AMD and the lack of effect found for treatment is inconsistent with those reports.\(^23\) One recently published study\(^35\) has reported more rapid progression in AMD in association with higher levels of C-reactive protein and interleukin 6. Unopposed estrogen treatment increases these inflammatory factors.\(^36\),\(^37\) While progestin may reduce some inflammatory factors,\(^38\)-\(^40\) Kwok et al\(^41\) reported a reduction in C-reactive protein levels among those given CEE + P vs CEE alone. An inflammatory response to CEE may offer a possible explanation for the lack of benefit in the CEE trial and potential benefits in the CEE + P trial.

We did not find clear benefits for early or late AMD related to treatment with either form of HT in the WHI HT CT. There is some suggestion of a benefit for neovascular disease or soft drusen, but study limitations preclude a definitive statement. Because the study was primarily powered to evaluate combined treatment and any AMD, our results for this outcome do not suggest the study was underpowered but that the treatment may not influence that outcome. Power was too limited to examine late-stage disease.

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